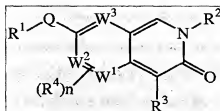


CLAIMS

What is claimed is:

5

1. A compound of Formula I



I

or a pharmaceutically acceptable salt thereof,
wherein:

10

R¹ is independently selected from:

- C₅ or C₆ cycloalkyl-(C₁-C₈ alkylenyl);
- Substituted C₅ or C₆ cycloalkyl-(C₁-C₈ alkylenyl);
- C₈-C₁₀ bicycloalkyl-(C₁-C₈ alkylenyl);
- Substituted C₈-C₁₀ bicycloalkyl-(C₁-C₈ alkylenyl);
- 5- or 6-membered heterocycloalkyl-(C₁-C₈ alkylenyl);
- Substituted 5- or 6-membered heterocycloalkyl-(C₁-C₈ alkylenyl);
- 8- to 10-membered heterobicycloalkyl-(C₁-C₈ alkylenyl);
- Substituted 8- to 10-membered heterobicycloalkyl-(C₁-C₈ alkylenyl);
- Phenyl-(C₁-C₈ alkylenyl);
- Substituted phenyl-(C₁-C₈ alkylenyl);
- Naphthyl-(C₁-C₈ alkylenyl);
- Substituted naphthyl-(C₁-C₈ alkylenyl);
- 5- or 6-membered heteroaryl-(C₁-C₈ alkylenyl);
- Substituted 5- or 6-membered heteroaryl-(C₁-C₈ alkylenyl);
- 8- to 10-membered heterobiaryl-(C₁-C₈ alkylenyl); and
- Substituted 8- to 10-membered heterobiaryl-(C₁-C₈ alkylenyl);
- Phenyl;
- Substituted phenyl;
- Naphthyl;
- Substituted naphthyl;

30

5- or 6-membered heteroaryl;
 Substituted 5- or 6-membered heteroaryl;
 8- to 10-membered heterobiaryl;
 Substituted 8- to 10-membered heterobiaryl;

5 R² is independently selected from:

H;
 C₁-C₆ alkyl;
 Phenyl-(C₁-C₈ alkylenyl);
 Substituted phenyl-(C₁-C₈ alkylenyl);
 10 Naphthyl-(C₁-C₈ alkylenyl);
 Substituted naphthyl-(C₁-C₈ alkylenyl);
 5- or 6-membered heteroaryl-(C₁-C₈ alkylenyl);
 Substituted 5- or 6-membered heteroaryl-(C₁-C₈ alkylenyl);
 8- to 10-membered heterobiaryl-(C₁-C₈ alkylenyl); and
 15 Substituted 8- to 10-membered heterobiaryl-(C₁-C₈ alkylenyl);
 Phenyl-O-(C₁-C₈ alkylenyl);
 Substituted phenyl-O-(C₁-C₈ alkylenyl);
 Phenyl-S-(C₁-C₈ alkylenyl);
 Substituted phenyl-S-(C₁-C₈ alkylenyl);
 20 Phenyl-S(O)-(C₁-C₈ alkylenyl);
 Substituted phenyl-S(O)-(C₁-C₈ alkylenyl);
 Phenyl-S(O)₂-(C₁-C₈ alkylenyl);
 Substituted phenyl-S(O)₂-(C₁-C₈ alkylenyl);

Each substituted R¹ and R² group contains from 1 to 4 substituents, each
 25 independently on a carbon or nitrogen atom, independently selected from:

C₁-C₆ alkyl;
 CN;
 CF₃;
 HO;
 30 (C₁-C₆ alkyl)-O;
 (C₁-C₆ alkyl)-S(O)₂;
 H₂N;
 (C₁-C₆ alkyl)-N(H);

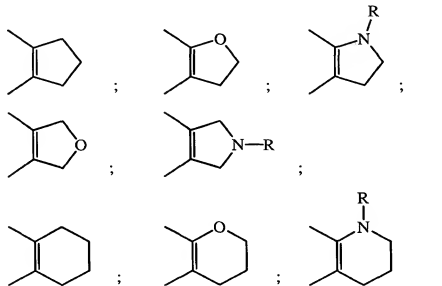
$(C_1-C_6 \text{ alkyl})_2-N$;
 $(C_1-C_6 \text{ alkyl})-C(O)O-(C_1-C_8 \text{ alkylenyl})_m$;
 $(C_1-C_6 \text{ alkyl})-C(O)O-(1- \text{ to } 8\text{-membered heteroalkylenyl})_m$;
 $(C_1-C_6 \text{ alkyl})-C(O)N(H)-(C_1-C_8 \text{ alkylenyl})_m$;
5 $(C_1-C_6 \text{ alkyl})-C(O)N(H)-(1- \text{ to } 8\text{-membered heteroalkylenyl})_m$;
 $H_2NS(O)_2-(C_1-C_8 \text{ alkylenyl})$;
 $(C_1-C_6 \text{ alkyl})-N(H)S(O)_2-(C_1-C_8 \text{ alkylenyl})_m$;
 $(C_1-C_6 \text{ alkyl})_2-NS(O)_2-(C_1-C_8 \text{ alkylenyl})_m$;
3- to 6-membered heterocycloalkyl-(G)_m;
10 Substituted 3- to 6-membered heterocycloalkyl-(G)_m;
5- or 6-membered heteroaryl-(G)_m; and
Substituted 5- or 6-membered heteroaryl-(G)_m;
 $(C_1-C_6 \text{ alkyl})-S(O)_2-N(H)-C(O)-(C_1-C_8 \text{ alkylenyl})_m$;
 $(C_1-C_6 \text{ alkyl})-C(O)-N(H)-S(O)_2-(C_1-C_8 \text{ alkylenyl})_m$;

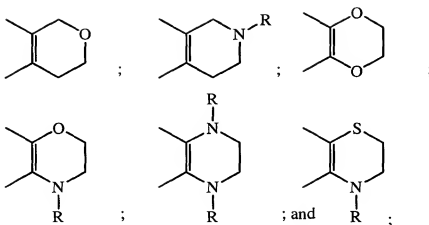
15 wherein each substituent on a carbon atom may further be independently selected from:

Halo; and
HO₂C;

20 wherein 2 substituents may be taken together with a carbon atom to which they are both bonded to form the group C=O;

wherein two adjacent, substantially sp² carbon atoms may be taken together with a diradical substituent to form a cyclic diradical selected from:





R is H or C₁-C₆ alkyl;

G is CH₂; O, S, S(O); or S(O)₂;

5 Each m is an integer of 0 or 1;

R³ is selected from the groups:

H;

C₁-C₆ alkyl;

Substituted C₁-C₆ alkyl;

10 C₂-C₆ alkenyl;

Substituted C₂-C₆ alkenyl;

C₂-C₆ alkynyl;

Substituted C₂-C₆ alkynyl;

C₃-C₆ cycloalkyl;

15 Substituted C₃-C₆ cycloalkyl;

C₃-C₆ cycloalkyl-(C₁-C₈ alkylenyl);

Substituted C₃-C₆ cycloalkyl-(C₁-C₈ alkylenyl);

Phenyl;

Substituted phenyl;

20 Phenyl-(C₁-C₈ alkylenyl);

Substituted phenyl-(C₁-C₈ alkylenyl);

Naphthyl;

Substituted Naphthyl;

Naphthyl-(C₁-C₈ alkylenyl);

25 Substituted naphthyl-(C₁-C₈ alkylenyl);

3- to 6-membered heterocycloalkyl;

Substituted 3- to 6-membered heterocycloalkyl;

3- to 6-membered heterocycloalkyl-(C₁-C₈ alkylenyl);

Substituted 3- to 6-membered heterocycloalkyl-(C₁-C₈ alkylenyl)

HO;

5 (C₁-C₆ alkyl)-O;

H₂N;

(C₁-C₆ alkyl)-N(H);

(C₁-C₆ alkyl)₂-N;

Each substituted R³ group contains from 1 to 4 substituents, each independently
10 on a carbon or nitrogen atom, independently selected from:

H₂N;

C₁-C₆ alkyl;

CN;

CF₃;

15 (C₁-C₆ alkyl)-OC(O);

HO;

(C₁-C₆ alkyl)-O;

HS; and

(C₁-C₆ alkyl)-S;

20 wherein each substituent on a carbon atom may further be independently selected from:

Halo; and

HO₂C;

wherein 2 substituents may be taken together with a carbon atom to which they
25 are both bonded to form the group C=O;

R⁴ is H, C₁-C₆ alkyl, H₂N, HO, or halo;

n is an integer of from 0 to 3;

Q is selected from:

OC(O);

30 CH(R⁵)C(O);

OC(NR⁵);

CH(R⁵)C(NR⁵);

N(R⁵)C(O);

$N(R^5)C(S)$;

$N(R^5)C(NR^5)$;

$N(R^5)CH_2$;

$SC(O)$;

5 $CH(R^5)C(S)$;

$SC(NR^5)$;

$trans-(H)C=C(H)$;

$cis-(H)C=C(H)$;

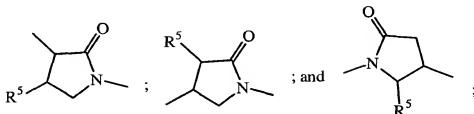
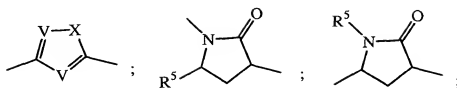
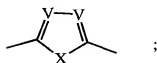
$C\equiv C$;

10 $CH_2C\equiv C$;

$C\equiv CCH_2$;

$CF_2C\equiv C$; and

$C\equiv CCF_2$;



15

R^5 is H, C_1 - C_6 alkyl, C_3 - C_6 cycloalkyl; 3- to 6-membered heterocycloalkyl;

phenyl; benzyl; or 5- or 6-membered heteroaryl;

X is O, S, N(H), or $N(C_1$ - C_6 alkyl);

Each V is independently C(H) or N;

20 Each W^1 , W^2 , and W^3 is independently N or $C-R^4$, wherein R^4 is as defined above;

wherein each C_8 - C_{10} bicycloalkyl is a bicyclic carbocyclic ring that contains 8-, 9-, or 10-member carbon atoms which are 5,5-fused, 6,5-fused, or 6,6-fused bicyclic rings, respectively, and wherein the ring is saturated or optionally contains one carbon-carbon double bond;

wherein each 8- to 10-membered heterobicycloalkyl is a bicyclic ring that contains carbon atoms and from 1 to 4 heteroatoms independently selected from 2 O, 1 S, 1 S(O), 1 S(O)₂, 1 N, 4 N(H), and 4 N(C₁-C₆ alkyl), and wherein when two O atoms or one O atom and one S atom are present, the two O atoms or one O atom and one S atom are not bonded to each other, and wherein the ring is saturated or optionally contains one carbon-carbon or carbon-nitrogen double bond, and wherein the heterobicycloalkyl is a 5,5-fused, 6,5-fused, or 6,6-fused bicyclic ring, respectively,

wherein each heterocycloalkyl is a ring that contains carbon atoms and from 1 to 4 heteroatoms independently selected from 2 O, 1 S, 1 S(O), 1 S(O)₂, 1 N, 4 N(H), and 4 N(C₁-C₆ alkyl), and wherein when two O atoms or one O atom and one S atom are present, the two O atoms or one O atom and one S atom are not bonded to each other, and wherein the ring is saturated or optionally contains one carbon-carbon or carbon-nitrogen double bond;

wherein each 5-membered heteroaryl contains carbon atoms and from 1 to 4 heteroatoms independently selected from 1 O, 1 S, 1 N(H), 1 N(C₁-C₆ alkyl), and 4 N, and each 6-membered heteroaryl contains carbon atoms and 1 or 2 heteroatoms independently selected from N, N(H), and N(C₁-C₆ alkyl), and 5- and 6-membered heteroaryl are monocyclic rings;

wherein each heterobiaryl contains carbon atoms and from 1 to 4 heteroatoms independently selected from 1 O, 1 S, 1 N(H), 1 N(C₁-C₆ alkyl), and 4 N, and where the 8-, 9-, and 10-membered heterobiaryl are 5,5-fused, 6,5-fused, and 6,6-fused bicyclic rings, respectively, and wherein at least 1 of the 2 fused rings of a bicyclic ring is aromatic, and wherein when the O and S atoms both are present, the O and S atoms are not bonded to each other;

wherein with any (C₁-C₆ alkyl)₂-N group, the C₁-C₆ alkyl groups may be optionally taken together with the nitrogen atom to which they are attached to form a 5- or 6-membered heterocycloalkyl; and

wherein each group and each substituent recited above is independently selected.

2. The compound according to Claim 1, or a pharmaceutically acceptable salt thereof, wherein W¹, W², and W³ are each C-R⁴, wherein R⁴ is as defined above.

3. The compound according to Claim 1, or a pharmaceutically acceptable salt thereof, wherein one of W^1 , W^2 , and W^3 is N and the other two of W^1 , W^2 , and W^3 are each $C-R^4$, wherein R^4 is as defined above.

5

4. The compound according to Claim 1, or a pharmaceutically acceptable salt thereof, wherein Q is $N(R^5)C(O)$ or $C\equiv C$.

10

5. The compound according to Claim 1, or a pharmaceutically acceptable salt thereof, wherein Q is $C\equiv C$.

6. The compound according to Claim 1, or a pharmaceutically acceptable salt thereof, wherein n is 0.

15

7. The compound according to Claim 1, or a pharmaceutically acceptable salt thereof, wherein n is 1.

20

8. The compound according to any one of Claims 1 to 7, or a pharmaceutically acceptable salt thereof, wherein R^1 is independently selected from:

- 5- or 6-membered heteroaryl-(C_1 - C_8 alkylenyl);
- Substituted 5- or 6-membered heteroaryl-(C_1 - C_8 alkylenyl);
- 8- to 10-membered heterobiaryl-(C_1 - C_8 alkylenyl);
- Substituted 8- to 10-membered heterobiaryl-(C_1 - C_8 alkylenyl);
- 25 Phenyl-(C_1 - C_8 alkylenyl); and
- Substituted phenyl-(C_1 - C_8 alkylenyl); and

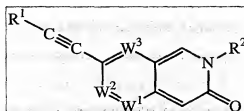
R^2 is independently selected from:

- 5- or 6-membered heteroaryl-(C_1 - C_8 alkylenyl);
- Substituted 5- or 6-membered heteroaryl-(C_1 - C_8 alkylenyl);
- 30 8- to 10-membered heterobiaryl-(C_1 - C_8 alkylenyl);
- Substituted 8- to 10-membered heterobiaryl-(C_1 - C_8 alkylenyl);
- Phenyl-(C_1 - C_8 alkylenyl); and

Substituted phenyl-(C₁-C₈ alkylenyl);

wherein each group and each substituent is independently selected.

9. The compound of Claim 1 of Formula II



II

or a pharmaceutically acceptable salt thereof.

10. The compound according to Claim 9, selected from:

4-[3-Oxo-7-(3-phenyl-prop-1-ynyl)-2H-isoquinolin-2-ylmethyl]benzoic acid tert-butyl ester;

4-[3-Oxo-7-(3-phenyl-prop-1-ynyl)-2H-isoquinolin-2-ylmethyl]benzoic acid;

2-(3,5-Difluoro-4-hydroxybenzyl)-7-[3-(4H-[1,2,3]triazol-4-yl)prop-1-ynyl]-2H-isoquinolin-3-one;

7-(3-Phenyl-prop-1-ynyl)-2-(4-trifluoromethylbenzyl)-2H-isoquinolin-3-one;

2-(3-Fluorobenzyl)-7-(3-phenyl-prop-1-ynyl)-2H-isoquinolin-3-one;

4-[7-(3-Imidazol-1-ylprop-1-ynyl)-3-oxo-2H-isoquinolin-2-ylmethyl]benzoic acid tert-butyl ester;

4-[7-(3-Imidazol-1-ylprop-1-ynyl)-3-oxo-2H-isoquinolin-2-ylmethyl]benzoic acid;

3-[3-Oxo-7-(3-phenyl-prop-1-ynyl)-2H-isoquinolin-2-ylmethyl]benzonitrile;

4-[3-Oxo-7-(3-phenyl-prop-1-ynyl)-2H-isoquinolin-2-ylmethyl]benzenesulfonamide;

4-[3-Oxo-7-(3-[1,2,3]triazol-1-ylprop-1-ynyl)-2H-isoquinolin-2-ylmethyl]benzoic acid tert-butyl ester;

4-[3-Oxo-7-(3-[1,2,3]triazol-1-ylprop-1-ynyl)-2H-isoquinolin-2-ylmethyl]benzoic acid;

4-[3-Oxo-7-(3-phenyl-prop-1-ynyl)-2H-isoquinolin-2-ylmethyl]benzoic acid methyl ester;

3-[3-Oxo-7-(3-phenyl-prop-1-ynyl)-2H-isoquinolin-2-ylmethyl]benzoic acid methyl ester;

5 2-(4-Fluorobenzyl)-7-3-phenylprop-1-ynyl-2H-isoquinolin-3-one;

7-(3-Phenylprop-1-ynyl)-2-(3-trifluoromethylbenzyl)-2H-isoquinolin-3-one;

2-(3-Chlorobenzyl)-7-(3-phenylprop-1-ynyl)-2H-isoquinolin-3-one;

10 2-(3,4-Difluorobenzyl)-7-(3-phenylprop-1-ynyl)-2H-isoquinolin-3-one;
and

4-[1-Oxo-7-(3-[1,2,4]triazol-1-ylprop-1-ynyl)-2H-isoquinolin-3-ylmethyl]benzoic acid tert-butyl ester; or

a pharmaceutically acceptable salt thereof.

15 11. A pharmaceutical composition, comprising a compound according to Claim 1, or a pharmaceutically acceptable salt thereof, admixed with a pharmaceutically acceptable carrier, excipient, or diluent.

20 12. The pharmaceutical composition according to Claim 11, comprising a compound according to Claim 10, or a pharmaceutically acceptable salt thereof, admixed with a pharmaceutically acceptable carrier, excipient, or diluent.

25 13. A method for treating osteoarthritis or rheumatoid arthritis, comprising administering to a patient suffering from osteoarthritis a nontoxic effective amount of a compound according to Claim 1, or a pharmaceutically acceptable salt thereof.

30 14. The method according to Claim 13, wherein the compound administered is a compound according to Claim 10, or a pharmaceutically acceptable salt thereof.